JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 12, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.08.003

EDITORIAL COMMENT

Age, Ethnicity, and Stroke Risk in Patients With Atrial Fibrillation

Another Stitch in the Patchwork*

John A. Savino III, MD, Jonathan L. Halperin, MD

The frequency with which clinicians encounter patients with nonvalvular atrial fibrillation (AF) and its association with ischemic stroke make estimation of the risk borne by individuals a daily issue in contemporary cardiology practice across the globe. In the balance lies the decision to employ long-term anticoagulation therapy with its attendant risk of severe bleeding. A variety of clinical risk scores are available to guide this decision, most prominently the CHA_2DS_2-VASc score, which cumulates the widely accepted, if unequally validated, clinical risk factors: heart failure (or impaired left ventricular function), hypertension, age, prior stroke (or transient ischemic attack or systemic thromboembolism), atherosclerotic vascular disease (as manifested by myocardial infarction, peripheral artery disease, or morphologically complex aortic atheroma), and female sex (1). Other scores recognize impaired renal function or other variables (2), and some emerging risk stratification approaches incorporate biomarkers, imaging of the morphology or flow properties of the left atrial appendage, and other considerations into the anticoagulation decision.

For over 20 years, however, patient age has been recognized as a consistent independent risk factor for stroke that carries an incremental relative risk of about 1.5 (95% confidence interval: 1.3 to 1.7) per decade (3,4). Although stroke prevention trials have increasingly been conducted on the international stage, much of the data from which clinical risk stratification schemes derive were acquired in Western, mainly Caucasian patient cohorts. In this issue of the *Journal,* Chao et al. (5) report on the differential risk of ischemic stroke in patients of Taiwanese origin with AF stratified according to the CHA_2DS_2-VASc

SEE PAGE 1339

criteria as at relatively low risk (CHA_2DS_2-VASc of 0 for men, 1 for women) (5). On the basis of approximately 9,400 men and 6,400 women with AF in a national registry, the main finding is that the risk of stroke in patients with AF but no CHA_2DS_2-VASc risk factors other than sex is higher among Taiwanese adults than previously recognized, with the important implication that stroke risk is subject to variation by ethnicity. Heretofore, ethnic differences have not been specifically incorporated into clinical practice guidelines, due mainly to paucity of data.

Several recent studies have reported wide variations in stroke risk among cohorts with low CHA_2DS_2-VASc risk scores. Stroke rates in a Danish cohort (6) (0.66%/year for men with a CHA_2DS_2-VASc score of 0 and 0.82%/year for women with scores of 1) were substantially higher than in a similar Swedish cohort, where rates were about 0.2%/year (7). Low rates have also been reported from the United States (2), whereas another analysis found the Taiwanese population at higher risk (8). The authors point out consistently increased risks of ischemic stroke in the Asian cohorts of RE-LY (Randomized Evaluation of Long-Term Anti-coagulation Therapy), ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), and ARISTOTLE (Apixaban for

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Cardiovascular Institute, Mount Sinai Medical Center, New York, New York. Dr. Savino has reported that he has no relationships relevant to the contents of this paper to disclose. Dr. Halperin has served as a consultant to Boehringer Ingelheim, Daiichi-Sankyo, Janssen, Pfizer, AstraZeneca, Biotronik, Boston Scientific, and Medtronic for advisory activities involving the development of anticoagulant drugs and other strategies to prevent stroke in patients with atrial fibrillation.

Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and the new data they provide suggests that a lower age threshold may be appropriate for selecting patients of Taiwanese ethnicity for anticoagulation.

It is important to bear in mind, though, that optimum treatment cannot be determined without prospective studies. Indeed, even assuming that the risk of bleeding is lower among younger patients, it is uncertain whether the cut-point should bet set at 50, 55, or 60 years, or some intermediate age. We should also be cautious in extrapolating the findings to other Asian populations. And although ethnicity seems pertinent, a host of clinical factors must be considered in the decision to employ long-term anticoagulation, not only those contributing to the thromboembolic and hemorrhagic risks, but also differences in response to the array of anticoagulant drugs that are now available, some of which are influenced by genetics and ethnicity (9,10).

Even more fundamental is the lack of information about the role of AF in the interplay between age and stroke risk. Does the risk of stroke among otherwise low-risk Taiwanese individuals without AF differ from people of other ethnic backgrounds? Evidence is accumulating that the CHA_2DS_2-VASc score, as well as other risk stratification schemes that are useful for patients with AF, can be applied with similar predictive value to assess the risk of stroke in patients without AF (11,12). Furthermore, specific genetic markers may be closely linked to stroke risk (13).

For patients with AF in whom the decision to employ anticoagulant medication hovers near the margin of risk and benefit, physicians must consider more than age and other risk factors for thromboembolism and bleeding. We must engage in a dialogue that acknowledges ethnicity, cultural and personal values, preferences, and social factors to ensure a balanced, comprehensive assessment that enhances adherence, safety, and clinical outcomes. Ethnicity is another piece of the puzzle, but exactly how to integrate this variable into clinical care will require innovative approaches to clinical research utilizing techniques of network biology to identify pathways or gene sets linked to the pathogenesis of atrial fibrillation and thromboembolism.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jonathan L. Halperin, The Cardiovascular Institute, Mount Sinai Medical Center, Fifth Avenue at 100th Street, New York, New York 10029. E-mail: jonathan.halperin@mssm.edu.

REFERENCES

1. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–72.

2. Singer DE, Chang Y, Borowsky LH, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc 2013;2:e000250.

3. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449–57.

4. Hart RG, Albers GW, Connolly SJ, et al., for the Stroke Risk in Atrial Fibrillation Working Group. Prediction of stroke in patients with atrial fibrillation: systematic review of independent predictors and absolute stroke rates. Neurology 2007;69:546–54.

5. Chao T-F, Wang K-L, Liu C-J, et al. Age threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. J Am Coll Cardiol 2015;66:1339–47.

6. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:dl24.

7. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA_2DS_2-VASc score of 1. J Am Coll Cardiol 2015;65:225–32.

8. Chao T-F, Liu C-J, Wang K-L, et al. Should atrial fibrillation patients with 1 additional risk factor of the CHA_2DS_2-VASc score (beyond sex) receive oral anticoagulation? J Am Coll Cardiol 2015;65:635–42.

9. Hori M, Connolly SJ, Zhu J, et al., for the RE-LY Investigators. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke 2013;44:1891–6.

10. Hori M, Matsumoto M, Tanahashi N, et al., for the J-ROCKET AF Study Investigators. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation: the J-ROCKET AF study. Circ J 2012;76:2104–11.

11. Lip GY, Lin HJ, Chien KL, et al. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. Int J Cardiol 2013;168:414–9.

12. Glotzer TV, Hellkamp AS, Lee KL, et al. CHA2DS2-VASC and CHADS2 scores predict adverse clinical events in patients with pacemakers and sinus node dysfunction independent of atrial fibrillation. Can J Cardiol 2015;31:1004–11.

13. Auer PL, Nalls M, Meschia JF, et al., for the National Heart, Lung, and Blood Institute Exome Sequencing Project. Rare and coding region genetic variants associated with risk of ischemic stroke: the NHLBI Exome Sequence Project. JAMA Neurol 2015;72:781–8.

KEY WORDS atrial fibrillation, CHA_2DS_2-VASc score, ischemic stroke, risk assessment, Taiwan